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Optimal high-density lipoprotein cholesterol cutoff for predicting cardiovascular disease: Comparison of the Korean and US National Health and Nutrition Examination Surveys

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BACKGROUND: Serum high-density lipoprotein cholesterol (HDL-C) has been reported to be lower in Asians than in Caucasians.

OBJECTIVE: We compared HDL-C levels between the Korean and US populations using stratified analysis according to age and sex and estimated the optimal cutoff value for HDL-C that best predicts the risk of cerebrovascular accidents (CVAs) and ischemic heart disease (IHD) in Koreans.

METHODS: The Korean National Health and Nutrition Examination Survey (KNHANES) 2010-2012 and the National Health and Nutrition Examination Survey (NHANES) 2011-2012 were used for the Korean and US populations, respectively. HDL-C levels were compared using general linear models. To estimate the optimal HDL-C cutoff value that predicts CVAs and IHD, sensitivity and specificity of different HDL-C levels were calculated.

RESULTS: The mean HDL-C level was significantly lower in KNHANES in both sexes (46.1 [standard error, 0.2] mg/dL in KNHANES and 47.7 [0.5] mg/dL in NHANES, $P = .003$ in men, and 51.2 [0.2] mg/dL in KNHANES and 58.3 [0.8] mg/dL in NHANES, $P < .001$ in women). The optimal HDL-C cutoff to predict CVA-IHD was 43 mg/dL and 48 mg/dL for Korean men and women, respectively, and 41 mg/dL and 56 mg/dL for US men and women, respectively.

CONCLUSION: HDL-C levels are significantly lower in both sexes in the Korean population than the US population. The optimal cutoff HDL-C value to predict the risk of CVA-IHD was 43 mg/dL for men and 48 mg/dL for women in the Korean population.

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Metabolic syndrome is a condition characterized by the presence of multiple metabolic risk factors for cardiovascular disease.[1] Low levels of high-density lipoprotein cholesterol (HDL-C), which is a component of metabolic syndrome, are associated with an elevated risk of atherosclerotic disorders such as cerebrovascular accidents

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(CVAs)[2] and ischemic heart disease (IHD).[3,4] The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III adopted HDL-C levels of <40 mg/dL in men and <50 mg/dL in women to indicate the cutoff for low HDL-C in metabolic syndrome[5] based on epidemiologic studies conducted in insulin resistant men[6] and women.[7,8] However, the inverse association between HDL-C concentrations and IHD risk is continuous, and a threshold relationship has not yet been identified.[9] Despite this limitation, this HDL-C cutoff is frequently used to estimate the risk of several metabolic and cardiovascular diseases in Korea.[10–12]

Interestingly, nationwide surveys conducted in the Korean and US populations have shown that the prevalence of low HDL-C in the Korean population is significantly higher than that in the US population, especially in women.[13] In the Korean National Health and Nutrition Examination Survey (KNHANES) 2001-2007, 59.3% to 61.2% of Korean women had low HDL-C, which was almost double that of US women (33.8%) in the National Health and Nutrition Examination Survey (NHANES) 1998-2006.[13] However, the incidence of cardiovascular disease in the Korean population is not higher than that in the US population.[14]

Serum HDL-C concentrations differ by ethnicity, with reportedly lower HDL-C levels in Asians than in Caucasians.[15] Furthermore, in the Korean population, the sex difference in HDL-C levels may not be as significant. On average, HDL-C levels are 10 mg/dL lower in adult Caucasian men than in Caucasian women[9,16]; however, the difference in mean (standard error [SE]) HDL-C levels between sexes was lower in KNHANES 2005 (43.8 [0.2] and 46.3 [0.2] mg/dL in men and women, respectively).[17]

Considering the ethnic differences in HDL-C, the estimation of an adequate cutoff for low HDL-C level to predict cardiovascular disease in the Korean population is important for the prevention and management of cardiovascular disease. However, there have been few studies to investigate HDL-C levels for this purpose in the Korean population. In the present study, we compared HDL-C levels based on the presence of CVA and IHD between the Korean and US populations using nationwide surveys conducted in the early 2010s. In addition, we estimated the cutoff value for HDL-C that best predicts the risk of CVA and IHD in the Korean population.

Methods

Subjects

The Korean Ministry of Health and Welfare designed the KNHANES, which has been conducted since 1998, to be representative of the Korean population using a stratified, multistage, probability sampling method; the survey has been described in detail elsewhere.[13,18] We analyzed data from the KNHANES V, which was conducted from January 2010 to December 2012 with 25,533 individuals (participation rate, 80.8%), representing 11,400 households and 576 sampling frames.

For the analysis of the US population, the NHANES was used. It is a cross-sectional, nationwide study conducted by the Centers for Disease Control and Prevention (CDC) and is designed to evaluate the health and nutritional status of the noninstitutionalized US population. Further details are described elsewhere.[19] Data from NHANES 2011-2012 were used for analysis, including 9756 individuals.

Subjects aged ≥30 years with HDL-C measurement were included in the analysis. In KNHANES (n = 25,533), 17,292 (67.7%) subjects were aged ≥30 years, and serum HDL-C was measured in 15,074 (87.2% of age ≥30 years) subjects. In NHANES (n = 9756), 4566 (46.8%) subjects were aged ≥30 years, and 4033 (88.3% of age ≥30 years) measured HDL-C.

Measurement of metabolic parameters and disease definitions

Anthropometric and laboratory measurements in the KNHANES were as described in the following. Height was measured to the nearest 0.1 cm using a stadiometer (seca 210, seca, Hamburg, Germany), and weight was measured to the nearest 0.1 kg (GL-6000-20, G-tech, Uijeongbu City, Korea). Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2). Waist circumference was measured to the nearest 0.1 cm (seca 200, seca). A mercury sphygmomanometer (Baumanometer, Baum, Copiague, NY, USA) was used to measure blood pressure to the nearest 2 mm Hg.

Blood samples were drawn from the antecubital vein in the morning after fasting for at least 8 hours. Samples were properly processed, immediately refrigerated at 2°C to 8°C, and sent to a central laboratory. Total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and fasting glucose were measured enzymatically (Hitachi Automatic Analyzer 7600, Hitachi, Tokyo, Japan). Glycated hemoglobin was measured by high-performance liquid chromatography (HLC-723G7, Tosoh, Tokyo, Japan).

The revised HDL-C value was determined, following reference values from the Clinical and Laboratory Standards Institute for metrological traceability. To verify the accuracy of HDL-C, traceability analysis was conducted by KNHANES in 2013 to confirm the accuracy of HDL-C measurement. Difference of HDL-C values from Korean central laboratory and US CDC were 5.3% to 9.2% for 2008 to 2011, and 2.3% to 3.5% for 2012. For this reason, new regression formula of HDL-C was necessary to verify HDL-C value, especially for 2008 to 2011. Commutable frozen serum samples were taken according to Clinical and Laboratory Standards Institute guideline, and samples were sent to CDC. Samples were analyzed with gold-standard

method by isotope dilution-gas chromatography-mass spectrometry. Following obtained data from CDC and Korean central laboratory, the conversion rates were obtained with Passing and Bablok regression method. With revised HDL-C formula, bias was in range of 0.17 to 0.84 mg/dL. Samples in 2012 were verified in similar manner by Abell-Kendall method.

- Revised HDL-C (2010-2011) = 0.872 × HDL-C (2010-2011) + 6.162
- Revised HDL-C (2012) = 0.952 × HDL-C (2012) + 1.096

The definition of low HDL-C followed the criteria proposed by NCEP ATP III[5]: <40 mg/dL in men and <50 mg/dL in women. The cutoff for TGs and LDL-C were set at 200 and 160 mg/dL, respectively. CVA was determined when a subject was ever told that they had a stroke by a health care professional, and IHD was determined when a subject was ever told that they had coronary heart disease, angina, or a heart attack by a health care professional. Diabetes mellitus status was classified as follows: normal glucose tolerance (fasting glucose, <100 mg/dL), impaired fasting glucose (fasting glucose, ≥100 and <126 mg/dL), and diabetes mellitus (fasting glucose, ≥126 mg/dL, HbA1C ≥ 6.5%, taking oral diabetic medication, or taking insulin). Subjects with systolic blood pressure of ≥140 mm Hg, with diastolic blood pressure of ≥90 mm Hg, or taking antihypertensive medication were classified as hypertensive. Subjects who ever smoked <100 cigarettes were considered nonsmokers, and subjects who ceased smoking but smoked >100 cigarettes in the past were considered ex-smokers.

Statistical analyses

All statistical analyses were performed using a complex sample design using SPSS version 20.0 (IBM Co, Armonk, NY, USA). Stratification variables and sampling weights were used as designated in KNHANES and NHANES. The total sum of weights of KNHANES and NHANES were adjusted to be the same in each population for comparability. A general linear model, adjusted for age, was used to compare HDL-C levels between the surveys according to TG level, LDL-C level, hypertension, diabetes, and smoking status. To estimate the performance of each HDL-C cutoff value for predicting the risk of CVA and IHD, the odds ratio (OR), sensitivity, and specificity were calculated ranging from 35 to 60 mg/dL at 1 mg/dL intervals. The optimal cutoff value of HDL-C was determined using the Euclidean method[20] as the minimal $r\left(r=\sqrt{(1-\text{sensitivity})^2+(1-\text{specificity})^2}\right)$. For that analysis, subjects taking dyslipidemia medication or supplements were excluded.

All data are presented as mean (SE) for continuous variables and percentage (SE) for nominal variables. Statistical significance was defined as $P < .05$.

Results

Baseline characteristics and distribution of HDL-C in KNHANES and NHANES

The analysis included 15,074 and 4033 subjects from KNHANES V and NHANES 2011-2012, respectively.

The subjects in KNHANES (50.5 [0.2] years) were significantly younger than those in NHANES (52.7 [0.5] years; $P < .001$). They also had a significantly lower BMI ($P < .001$) and waist circumference ($P < .001$) than those in NHANES (Table 1). The prevalence of hypertension and diabetes were significantly lower in KNHANES ($P < .001$ and $P = .010$, respectively). Either CVA or IHD (CVA-IHD) also occurred less frequently in the subjects in KNHANES compared with those in NHANES ($P < .001$; Table 1). In terms of lipid profile, subjects in KNHANES showed a significantly higher LDL-C level ($P < .001$). Men in KNHANES had a higher TG level than men in NHANES ($P = .011$). Mean HDL-C was significantly lower in KNHANES than in NHANES in both sexes (46.1 [0.2] and 47.7 [0.5] mg/dL, respectively, $P = .003$ in men; 51.2 [0.2] and 58.3 [0.8] mg/dL, respectively, $P < .001$ in women; Table 1 and Supplementary Fig. 1). Based on the conventional NCEP ATP III criteria, 31.1% and 49.2% of Korean men and women, respectively, had low HDL-C, whereas 26.5% and 29.1% of US men and women, respectively, had low HDL-C. We subsequently estimated the proportion of subjects with variable HDL-C cutoff ranging from 35 to 60 mg/dL (Supplemental Table 1). The proportion of Korean women with HDL-C of ≤45 mg/dL was 31.3%, which was still higher than the proportion of US women with HDL-C of ≤50 mg/dL (Supplemental Table 1).

HDL-C was significantly lower in the subjects with a history of CVA-IHD in both sexes in both KNHANES and NHANES. In men in KNHANES, the mean HDL-C was 42.8 (0.7) mg/dL with CVA-IHD and 46.1 (0.2) mg/dL without CVA-IHD. In men in NHANES, the mean HDL-C was 46.3 (1.6) mg/dL with CVA-IHD and 47.9 (0.5) mg/dL without CVA-IHD (Table 2). The same trends were evident in women (Table 3). To reduce the confounder to clarify whether there is difference in reference level of HDL-C between KNHANES and NHANES, the HDL-C levels were compared between the surveys for each age group of subjects without CVA-IHD. Comparing HDL-C level between KNHANES and NHANES in each age group, the HDL-C levels in Korean women were lower than those in US women across all age groups (Table 3 and Supplementary Fig. 2). In men, significantly lower HDL-C levels were observed in Korean men only in the 60- to 69-year and 70- to 79-year groups (Table 2).

In both men and women in NHANES, HDL-C levels increased with increasing age (P for trend < .001 in men and P for trend = .004 in women; Tables 2 and 3). The relationship between age and HDL-C was the opposite in

Table 1 The baseline characteristics of KNHANES and NHANES subjects

Characteristics	KNHANES (2010-2012) N = 15,074	NHANES (2011-2012) N = 4033	*P* value
Weighted N	8.67×10^7	8.95×10^7	
Demographics			
Age, y	50.5 (0.2)	52.7 (0.5)	<.001
Gender (male), %	48.9 (0.3)	47.6 (1.0)	.210
Current smoker, %	25.6 (0.5)	19.3 (1.0)	<.001
Hypertension, %	28.9 (0.9)	37.6 (1.1)	<.001
Diabetes mellitus, %	10.2 (0.3)	12.0 (0.6)	.010
Lipid medication, %	5.8 (0.2)	21.8 (1.2)	<.001
Anthropometric measures			
Body weight, kg	63.7 (0.1)	81.6 (0.6)	<.001
Body mass index, kg/m^2	23.9 (0.0)	28.7 (0.2)	<.001
Waist circumference, cm	82.1 (0.1)	94.8 (0.7)	<.001
SBP, mm Hg	120.3 (0.2)	121.6 (0.8)	.093
DBP, mm Hg	77.4 (0.1)	71.0 (0.5)	<.001
Lipid profiles			
Total cholesterol, mg/dL	191.9 (0.4)	199.5 (1.1)	<.001
HDL-C, mg/dL	48.6 (0.1)	53.2 (0.5)	<.001
Male	46.1 (0.2)	47.7 (0.5)	.003
Female	51.2 (0.2)	58.3 (0.8)	<.001
Non–HDL-C, mg/dL	143.4 (0.4)	146.3 (1.0)	.011
Male	145.2 (0.6)	146.8 (1.0)	.023
Female	141.6 (0.5)	145.8 (1.2)	.014
TG, mg/dL	142.1 (1.4)	131.5 (4.5)	.023
Male	165.4 (2.1)	147.3 (6.7)	.011
Female	119.3 (1.4)	116.6 (3.9)	.518
LDL-C, mg/dL	117.2 (0.7)	110.1 (1.7)	<.001
Cardiovascular disease			
CVA-IHD, %	4.2 (0.2)	9.2 (0.2)	<.001
CVA, %	1.6 (0.1)	3.5 (0.4)	<.001
IHD, %	2.6 (0.2)	6.6 (0.4)	<.001

CVA, cerebrovascular accident; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IHD, ischemic heart disease; KNHANES, Korean National Health and Nutrition Examination Survey; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; TG, triglyceride.

Values are presented as mean or % (standard error).

Korean women (*P* for trend < .001), and the HDL-C levels were significantly lower than NHANES across all age groups. Subgroup analysis for menopause revealed that Korean women had lower HDL-C levels after menopause (*P* = .004, adjusted for age), which was not found in US women (*P* = .272, adjusted for age; Table 3). Of the Korean women, 8.2% were taking hormone replacement therapy (HRT) compared with 22.9% of US women. Excluding women taking HRT, Korean women continued to have lower HDL-C levels after menopause (*P* = .021, adjusted for age), whereas US women did not (*P* = .185, adjusted for age). In postmenopausal women, HDL-C decreased after excluding HRT in both populations (Korean, 49.8-49.6 mg/dL; US, 59.5-58.5 mg/dL). The association between age and HDL-C levels was not significant in Korean men.

Hypertriglyceridemia, hypertension, and diabetes affected HDL-C levels in both KNHANES and NHANES, although smoking status did not (Tables 2 and 3). As it is well-known that HDL-C is closely correlated with TGs,[21] we compared HDL-C only in the subjects with TG level of <200 mg/dL. In Korean men and women with TG level of <200 mg/dL, mean HDL-C was 47.9 (0.2) and 52.4 (0.2) mg/dL, respectively, which was significantly lower than that in US men and women with TG level of <200 mg/dL who had mean HDL-C levels of 50.4 (0.8) mg/dL (*P* = .003) and 60.6 (1.1) mg/dL, respectively (*P* < .001; Tables 2 and 3). Irrespective of the absence or presence of hypertension, subjects in NHANES showed significantly higher HDL-C levels than those in KNHANES. In subjects with diabetes, there was no difference in HDL-C levels between KNHANES and NHANES in both sexes, although the subjects with normal glucose tolerance or impaired fasting glucose in KNHANES showed significantly lower HDL-C levels than those in NHANES (Tables 2 and 3).

Table 2 The distribution of high-density lipoprotein cholesterol (HDL-C) by associated variables in men

Variables	KNHANES					NHANES					
	Total	CVA-IHD(−)	CVA-IHD(+)	*P* value*	*P* value†	Total	CVA-IHD(−)	CVA-IHD(+)	*P* value*	*P* value†	*P* value‡
Total	46.1 (0.2)	46.1 (0.2)	42.8 (0.7)	<.001		47.7 (0.5)	47.9 (0.5)	46.3 (1.6)	.032		.005
Age, y											
30-39	46.4 (0.4)	46.5 (0.4)	45.1 (1.3)	.587	.725	46.7 (0.7)	46.7 (0.6)	46.0 (7.7)	.923	<.001	.756
40-49	45.7 (0.3)	45.6 (0.3)	41.7 (0.3)	.043		45.9 (0.6)	46.1 (0.5)	41.9 (2.9)	.153		.726
50-59	46.0 (0.4)	46.2 (0.4)	41.0 (1.5)	.002		46.8 (1.0)	46.8 (1.0)	47.0 (2.9)	.936		.428
60-69	46.1 (0.4)	46.4 (0.4)	43.6 (0.9)	.008		51.1 (1.4)	51.5 (1.5)	49.2 (2.4)	.343		.001
70+	46.2 (0.4)	46.6 (0.5)	43.5 (1.0)	.007		49.8 (1.2)	52.2 (1.0)	45.1 (2.2)	.002		.004
Smoking											
Nonsmoker	45.9 (0.4)	46.0 (0.4)	43.6 (1.6)	.137	.439	46.9 (0.8)	46.9 (0.7)	46.5 (3.0)	.389	.362	.267
Ex-smoker	46.4 (0.3)	46.6 (0.3)	43.4 (0.9)	.001		48.5 (0.7)	49.0 (0.9)	45.6 (1.2)	.003		.006
Current smoker	45.7 (0.3)	45.9 (0.3)	41.3 (1.1)	<.001		48.1 (1.2)	48.3 (1.1)	47.2 (2.7)	.468		.041
TG											
<200	47.8 (0.2)	47.9 (0.2)	44.2 (0.7)	<.001	<.001	50.1 (0.8)	50.4 (0.8)	48.1 (2.3)	.141	<.001	.003
≥200	40.7 (0.3)	40.8 (0.3)	37.0 (1.0)	<.001		38.8 (0.8)	39.1 (1.0)	37.2 (1.4)	.322		.025
LDL-C											
<160	44.6 (0.3)	44.8 (0.3)	41.5 (1.1)	.006	.638	48.6 (0.7)	49.0 (0.7)	46.4 (2.1)	.093	.872	<.001
≥160	44.3 (0.7)	44.4 (0.7)	33.8 (2.1)	<.001		48.1 (1.2)	48.5 (1.2)	43.5 (3.9)	.244		.007
Hypertension											
No	45.7 (0.4)	45.9 (0.4)	44.9 (0.6)	.014	.192	47.5 (0.6)	47.5 (0.6)	48.1 (2.8)	.581	.454	.010
Yes	44.6 (0.5)	40.5 (2.1)	40.8 (1.2)	.005		47.9 (0.6)	48.4 (0.7)	45.6 (1.7)	.026		<.001
Diabetes											
NGT	46.5 (0.2)	46.6 (0.2)	42.9 (0.9)	<.001	<.001	49.3 (0.9)	49.1 (0.9)	52.2 (4.2)	.930	<.001	.006
IFG	45.6 (0.3)	45.6 (0.3)	42.1 (1.0)	<.001		48.8 (1.0)	49.1 (1.1)	47.0 (2.7)	.210		.003
DM	43.8 (0.5)	43.9 (0.6)	43.9 (1.7)	.904		43.0 (0.8)	43.8 (1.0)	40.3 (1.6)	.023		.647
Lipid medication											
No	46.1 (0.2)	46.2 (0.2)	45.3 (0.8)	<.001	.291	47.9 (0.5)	47.9 (0.6)	48.5 (2.9)	.573	.017	.005
Yes	44.4 (0.7)	44.7 (0.5)	43.1 (1.0)	.001		46.8 (0.7)	47.5 (0.8)	45.1 (1.6)	.103		.044

CVA, cerebrovascular accident; DM, diabetes mellitus; IFG, impaired fasting glucose; IHD, ischemic heart disease; KNHANES, Korean National Health and Nutrition Examination Survey; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; NHANES, National Health and Nutrition Examination Survey; TG, triglyceride.

Values are presented as mean (standard error) HDL-C in units of mg/dL.

*Comparing HDL-C between CVA-IHD(−) and CVA-IHD(+) in the same subgroup of a variable (adjusted for age).

†Comparing HDL-C according to each factor in subjects without CVA-IHD (adjusted for age); *P* for trend for age, smoking, and diabetes (adjusted for age).

‡Comparing HDL-C between KNHANES and NHANES only in subjects without CVA-IHD (adjusted for age).

Table 3 The distribution of high-density lipoprotein cholesterol (HDL-C) by associated variables in women

Variables	KNHANES					NHANES					
	Total	CVA-IHD(−)	CVA-IHD(+)	*P* value*	*P* value†	Total	CVA-IHD(−)	CVA-IHD(+)	*P* value*	*P* value†	*P* value‡
Total	51.2 (0.2)	51.3 (0.2)	47.6 (0.7)	.042		58.3 (0.8)	58.8 (0.8)	52.7 (1.0)	<.001		<.001
Age, y											
30-39	53.9 (0.3)	53.8 (0.3)	56.3 (3.1)	.434	<.001	56.2 (1.1)	56.2 (1.1)	55.3 (7.7)	.902	.004	.037
40-49	51.7 (0.3)	51.8 (0.3)	46.1 (2.7)	.035		56.3 (0.8)	56.6 (0.8)	48.3 (3.5)	.029		<.001
50-59	51.1 (0.3)	51.1 (0.3)	51.2 (1.8)	.993		60.3 (1.8)	60.8 (1.9)	49.7 (2.0)	.001		<.001
60-69	49.1 (0.4)	49.0 (0.3)	48.5 (1.4)	.720		60.5 (1.7)	61.3 (1.9)	52.8 (2.0)	.022		<.001
70+	46.8 (0.3)	47.2 (0.3)	44.4 (0.9)	.004		59.0 (1.2)	60.5 (1.4)	54.3 (1.8)	.013		<.001
Smoking											
Nonsmoker	51.0 (0.2)	51.2 (0.2)	47.7 (0.7)	.042	.285	58.3 (0.7)	58.5 (0.7)	54.7 (1.8)	.050	.723	<.001
Ex-smoker	52.6 (0.9)	53.0 (0.9)	43.3 (3.6)	.105		60.1 (1.2)	61.1 (1.4)	51.1 (2.4)	.001		<.001
Current smoker	52.2 (0.8)	52.3 (0.9)	49.4 (7.3)	.816		55.7 (1.5)	56.3 (1.6)	50.5 (1.9)	.004		.046
Menopause											
No	52.5 (0.2)	52.5 (0.2)	50.8 (2.0)	.513		56.2 (1.0)	56.3 (1.0)	53.3 (3.7)	.429		<.001
Yes	49.8 (0.2)	50.0 (0.2)	47.1 (0.8)	.069	.004	59.5 (1.2)	60.5 (1.3)	52.5 (1.2)	<.001	.272	<.001
Yes (no HRT)	49.6 (0.2)	49.8 (0.2)	46.8 (0.8)	.054	.021	58.5 (1.1)	59.2 (1.2)	53.2 (1.5)	.004	.185	<.001
TG											
<200	52.6 (0.2)	52.4 (0.2)	49.4 (0.7)	.215	<.001	60.3 (1.1)	60.6 (1.1)	57.9 (1.8)	.002	<.001	<.001
≥200	42.4 (0.4)	42.7 (0.4)	39.0 (1.2)	.019		45.4 (1.3)	46.3 (1.4)	39.3 (1.4)	.075		.025
LDL-C											
<160	49.2 (0.3)	49.3 (0.3)	45.7 (1.3)	.396	.002	58.8 (1.1)	59.0 (1.1)	56.5 (1.6)	.010	.211	<.001
≥160	50.8 (0.8)	51.1 (0.8)	41.5 (3.2)	.006		61.6 (2.0)	62.0 (2.2)	54.0 (5.0)	.117		<.001
Hypertension											
No	51.5 (0.3)	51.6 (0.3)	47.8 (0.5)	.213	.047	59.1 (0.9)	59.2 (0.9)	52.8 (2.9)	.013	.002	<.001
Yes	47.9 (0.5)	47.3 (2.1)	48.8 (1.9)	.446		57.2 (0.9)	58.0 (1.2)	52.7 (1.4)	.005		<.001
Diabetes											
NGT	52.1 (0.2)	52.2 (0.2)	48.1 (1.0)	.066	<.001	61.5 (1.0)	62.0 (0.9)	53.9 (2.2)	.001	<.001	<.001
IFG	49.1 (0.4)	49.2 (0.4)	47.5 (1.4)	.641		59.5 (1.4)	59.2 (1.4)	63.3 (3.2)	.791		<.001
DM	45.0 (0.6)	45.1 (0.6)	45.3 (1.8)	.763		47.8 (1.0)	47.7 (1.3)	48.4 (2.7)	.550		.060
Lipid medication											
No	51.3 (0.2)	51.4 (0.2)	47.8 (0.8)	.169	.738	58.8 (0.7)	58.9 (0.8)	56.2 (2.1)	.042	.015	<.001
Yes	49.0 (0.5)	49.4 (0.6)	46.9 (1.3)	.097		56.4 (1.2)	58.1 (1.5)	50.5 (1.2)	.003		<.001

CVA, cerebrovascular accident; DM, diabetes mellitus; HRT, hormone replacement therapy; IFG, impaired fasting glucose; IHD, ischemic heart disease; KNHANES, Korean National Health and Nutrition Examination Survey; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; NHANES, National Health and Nutrition Examination Survey; TG, triglyceride.

Values are presented as mean (standard error) HDL-C in units of mg/dL.

*Comparing HDL-C between CVA-IHD(−) and CVA-IHD(+) in the same subgroup of a variable (adjusted for age).

†Comparing HDL-C according to each factor in subjects without CVA-IHD (adjusted for age); *P* for trend for age, smoking, and diabetes (adjusted for age).

‡Comparing HDL-C between KNHANES and NHANES only in subjects without CVA-IHD (adjusted for age).

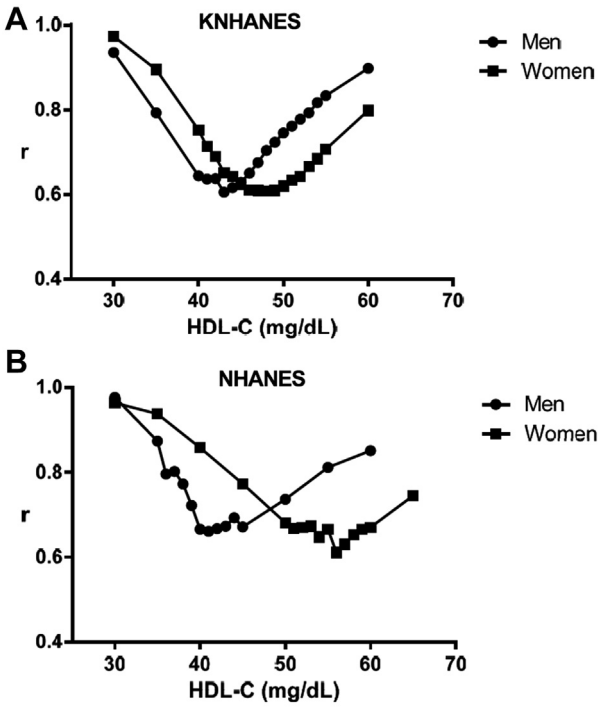

Figure 1 High-density lipoprotein cholesterol (HDL-C) cutoffs to predict cerebrovascular accidents (CVA) and ischemic heart disease (IHD) in the Korean population. The ability of identifying the risk of CVA-IHD using different cutoff values of HDL-C. KNHANES, Korean National Health and Nutrition Examination Survey; NHANES, National Health and Nutrition Examination Survey.

Optimal HDL-C cutoff values for predicting CVA and IHD

Considering the difference in HDL-C in subjects without CVA-IHD between KNHANES and NHANES, we investigated the optimal HDL-C cutoff values to predict CVA and IHD using the Euclidean method. The minimal *r* values for the prediction of CVA-IHD were 0.605 and 0.609 for Korean men and women, respectively, which corresponded to HDL-C levels of 43 mg/dL in men and 48 mg/dL in women (Fig. 1). Sensitivity and specificity of each HDL-C cutoff value were 58.2% and 56.2%, respectively, in Korean men and 56.8% and 57.1%, respectively, in Korean women. The ORs of the optimal HDL-C cutoff values to predict CVA-IHD were 1.78 (95% confidence interval [CI], 1.35-2.36) in Korean men and 1.75 (CI, 1.33-2.30) in Korean women. In US men and women, the minimal *r* values were 0.661 and 0.611, respectively, which corresponded to HDL-C levels of 41 and 56 mg/dL, respectively. Sensitivity and specificity of the HDL-C cutoff values were 41.0% and 70.3%, respectively, in US men, and 61.0% and 53.0%, respectively, in US women. The ORs of the optimal HDL-C cutoff values to predict CVA-IHD were 1.65 (CI, 0.88-3.10) in US men and 1.76 (CI, 0.96-3.05) in US women. Subgroup analysis for subjects with TG level of <200 mg/dL and without diabetes did not alter the optimal HDL-C cutoffs (data not shown).

We subsequently investigated the separate HDL-C cutoff values for CVA and IHD. The HDL-C cutoffs to predict CVA were 43 mg/dL (OR, 2.09; CI, 1.40-3.12) and 47 mg/dL (OR, 2.10; CI, 1.30-3.40) for Korean men and women, respectively, and 41 mg/dL (OR, 2.87; CI, 1.28-6.45) and 56 mg/dL (OR, 1.41; CI, 0.65-6.05) for US men and women, respectively. The HDL-C cutoffs for IHD were 43 mg/dL (OR, 1.58; CI, 1.10-2.27) and 49 mg/dL (OR, 1.56; CI, 1.08-2.25) for Korean men and women, respectively, and 47 mg/dL (OR, 1.38; CI, 0.75-2.52) and 56 mg/dL (OR, 1.78; CI, 0.72-4.39) for US men and women, respectively.

Considering the difference of HDL-C between the subjects with or without lipid medication, we analyzed the optimal HDL-C cutoffs in the entire population in predicting CVA-IHD. Including subjects taking lipid medication did not substantially alter HDL-C cutoffs except in US men: it increased from 41 to 43 mg/dL in US men (Supplementary Table 2).

Discussion

Using nationwide data sets representing the Korean and US populations, the present study confirmed that HDL-C levels in the Korean population were significantly lower than those in the US, by 1.6 mg/dL in men and 7.2 mg/dL in women. These results support those of a previous study that reported a higher prevalence of low HDL-C levels in the Korean population than the US population.[13] Furthermore, we estimated the optimal cutoff values for HDL-C to predict the prevalence of CVA-IHD, which were 43 mg/dL for Korean men, 48 mg/dL for Korean women, 41 mg/dL for US men, and 56 mg/dL for US women.

Low HDL-C level is a well-known risk predictor for stroke[2] and IHD,[3,4] although there has been little evidence that modifying HDL-C level itself provides benefit.[22] The most frequently used definition of low HDL-C level is based on the NCEP ATP III criteria; however, this is an arbitrary value, and the panel agrees that reexamination of the appropriate HDL-C cutoff is needed, as the association between HDL-C and cardiovascular risk is continuous, and inflection points are uncertain.[5] Furthermore, the low HDL-C cutoff in the NCEP ATP III definition of metabolic syndrome is based on the HDL-C distribution in Caucasians.[6–8] Considering that ethnicity affects serum HDL-C levels[13,15] and that the definition of metabolic syndrome is intended to identify individuals at cardiovascular risk,[1] the determination of optimal HDL-C cutoff values specifically for Asians is warranted.

Using the NCEP ATP III criteria, approximately 60% of Korean women have been previously identified with low HDL-C levels,[13] which seems unreasonably high. In the present study, the HDL-C levels in the Korean subjects without CVA-IHD were even slightly lower than those in the US subjects with a history of CVA-IHD. Especially in women, the differences in HDL-C levels between

KNHANES and NHANES were considerable at all ages. The present study analyzed data from a nationwide database, and the estimated HDL-C cutoffs resulted in 44.2% of men and 43.3% of women with low HDL-C levels.

Although we did not show a direct mechanism for the difference in HDL-C levels between the Korean and US populations, related factors can be inferred from previous studies. Genetic polymorphisms in *CETP*,[23] *ABCA1*,[24] *LIPC*,[25] and *PPARγ*[26] genes might explain the observed ethnic difference in HDL-C level, ie, *CETP* 451Q allele, which represents a significantly higher CETP activity and lower HDL-C levels, has not been found in Asian populations.[23] Along with genetic difference, environmental factors such as carbohydrate consumption can influence the HDL-C level.[27,28] Carbohydrates represent >70% of energy intake for Korean adults owing to the high carbohydrate content of the Korean traditional diet; the US population consumes less carbohydrates as a percentage of overall energy intake.[27,29] Further studies elucidating whether the ethnic difference in HDL-C level belongs to genetic difference or environmental factors are required, which might help to understand the clinical meaning of HDL-C level among the difference populations.

Interestingly, the relationships between age and HDL-C levels in women in the KNHANES and NHANES were opposite. HDL-C levels decreased with increasing age in Korean women and increased with increasing age in US women. Endogenous estrogen levels might explain these differences in HDL-C levels between the ethnic groups. Decreased endogenous estrogen is thought to reduce HDL-C, particularly subpopulation HDL_2, by affecting hepatic lipase activity.[30] In contrast, increasing estrogen levels through the administration of exogenous estrogen is known to increase HDL-C levels.[31] In the same vein, exclusion of subjects with HRT resulted in decreased HDL-C in postmenopausal women in both populations. In addition, estrogen-receptor polymorphisms affect the degree of HDL-C response to HRT.[32] The prevalence of numerous single-nucleotide polymorphisms on *ESR1* and *ESR2* has been reported to differ by ethnicity.[33] However, the effect of estrogen receptor polymorphisms on HDL-C has not been consistently reported; further independent studies should be performed.

Regarding the presence of diabetes, there were no differences in HDL-C levels between the Korean and US subjects with diabetes, even after adjustment for age and BMI. The main pathogenesis in diabetes is insulin resistance, which also lowers HDL-C levels and increases TG levels.[34] It appears as if the effect of insulin resistance on HDL-C is not affected by ethnic differences in HDL-C.

This study was performed using a nationwide survey, which included a large number of subjects representing each population. However, this study has certain limitations. First, the cross-sectional analysis did not allow causal relationships to be determined. Second, the questionnaires were self-administered, which could have resulted in recall bias. Third, differences in baseline characteristics including age, body weight, and lipid profiles limited direct comparisons of HDL-C levels between the populations. However, this did not affect the main purpose of this study, which was to investigate the epidemiologic distribution of HDL-C and the need for a different HDL-C cutoff value in the Korean population. Furthermore, the stratified analysis that accounted for confounders of HDL-C levels likely reduced the risk of error when comparing the KNHANES and NHANES data. However, the absolute r values, which were calculated to evaluate HDL-C as a predictor for CVA and IHD, were relatively high, with the majority at approximately 0.6. In addition, the sensitivity and specificity were approximately 60%. High r values indicate that HDL-C is not a good indicator for CVA or IHD as a single parameter. Therefore, other metabolic risk factors, such as age, body weight, other lipid indices, and genetic disposition, should also be considered in combination with HDL-C when evaluating cardiovascular risk.

Based on nationwide survey data in the Korean and US populations, HDL-C levels tended to be lower in Koreans, and the differences were more pronounced in women. The pattern of HDL-C levels through the life span varied by population. Considering the different HDL-C distributions by ethnicity, we suggest that lower HDL-C cutoffs to evaluate cardiovascular risk should be used for Korean women.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jacl.2015.01.009.

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